with cellular changes to chondrocytes, an increase in degradative stimuli and changes to the proteins of the extracellular matrix. It is not known to what extent these changes occur with age or if they are specific to diseased cartilage. Herein, we systematically investigated the changes that occur with age in mouse cartilage.

Methods: C57/BL (ICRFa) mice have been selectively bred for longevity. Knee joints were collected (4 mice/group) at 3, 6, 12, 24, 30 months of age. Histology *was* performed with sections stained with hematoxylin & eosin (H&E), safranin O, Picro-sirius red and antibodies to cleaved type II collagen, MMP13, nitro-tyrosine (as a measure of oxidative stress), cleaved LC3B (as a measure of autophagy) and Bcl-2 /Bax (as a measure of apoptosis).

Results: Our data indicate that a progressive degradation and loss of matrix occurs with age particularly in the load bearing area of cartilage. An increase in oxidative stress, MMP13 expression and type II collagen cleavage products occur with age with a concomitant decrease in autophagy and increase in apoptosis.

Conclusions: This study demonstrates that many of the changes that occur in osteoarthritis are found in cartilage with increasing age. The increase in the level of oxidative stress, MMP-13 and type II collagen cleavage products explain the complete loss of cartilage tissue from load bearing regions of the joint in 30 month old mice joints. These changes explain the marked predisposition to osteoarthritis with increasing age.

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CHANGES INDUCED BY CHRONIC *IN VIVO* LOAD ALTERATION IN THE TIBIO-FEMORAL JOINT OF MATURE RABBITS

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Purpose: This work determines the relationship between the magnitude and duration of chronic compressive load alteration and the development of degenerative changes in the rabbit tibio-femoral joint.

Methods: Twenty male skeletally-mature NZW rabbits, 12 months of age, mean weight 4.46±0.48 kg were randomized into one of 5 treatment groups: 0% BW-12wk (Sham), 50% BW-12wk, 80% BW-12wk, 50% BW-24wk, and 80% BW-24wk (n=4/group). NIH guidelines for the care and use of animals were observed. A varus loading device (VLD) was attached to the left hind limb to apply altered compressive loads of 0, 50 or 80% body weight (BW) to the tibio-femoral joint resulting in increased loading to the medial compartment and decreased loading to the lateral compartment. Altered loads were applied 12 hours per day for 12 or 24 weeks. Compartment-specific assessment of the tibial plateau from the experimental limb included histological assessments (OARSI degeneration score, articular cartilage, calcified cartilage, and subchondral bone thicknesses, and articular cartilage cellularity) and biomechanical measures (aggregate modulus and permeability). Analyses of variance techniques were used to examine the relationship between each outcome measure with load magnitude and duration as independent variables in the model.

Results: Degenerative changes developed in the medial compartment with increased magnitude of compressive loading (Fig. 1 & 2). The mean degeneration score in the 80% BW-24wk group increased 110% as compared to the 0% BW-12wk (Sham) group and 58% from the 80% BW-12wk group ($p < .01$ and $p = .01$; respectively). Similarly the 50% BW-12wk and 50% BW-24wk groups were increased as compared to the 0% BW-12wk group ($p = .04$ each). The mean cellularity varied with time across groups in the medial compartment ($p = .01$). Cellularity of the 50% BW-24wk group was decreased 22% as compared to the 50% BW-12wk group ($p = .03$). A similar decrease of 22% was observed for the 80% BW-24wk group as compared to the 80% BW-12wk group ($p = .08$). Increased calcified cartilage thickness was observed in both the medial and lateral compartments following exposure to altered loading of 80% BW for 24 weeks ($p < .05$ for each). Differences in aggregate modulus and permeability across groups did not reach statistical significance.

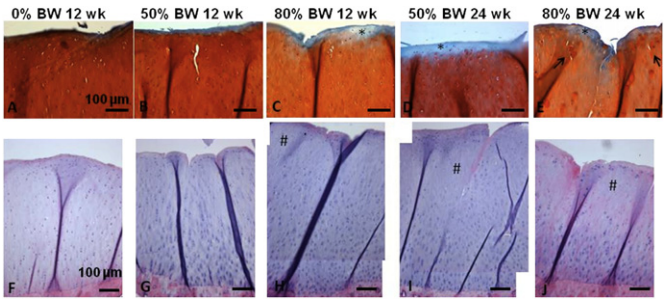

Fig. 1. Representative sections of the medial compartment stained with Safranin-O (A-E) and H&E (F-J); * loss of proteoglycan staining, –> chondrocyte hypertrophy, # decreased cellularity.

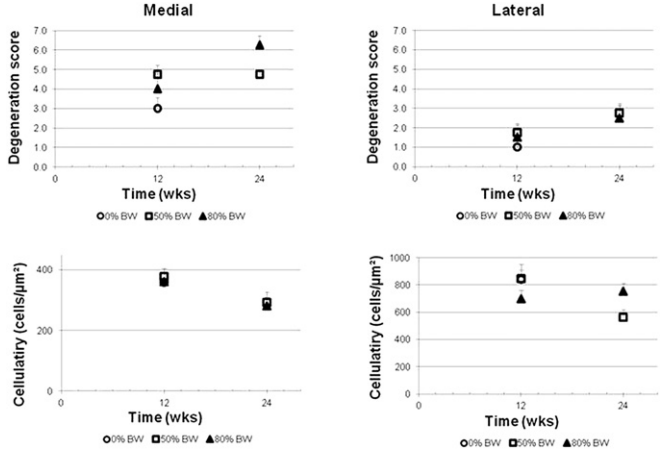

Fig. 2. Mean degeneration score and cellularity of the medial and lateral compartments.

Conclusions: This work demonstrates that *in vivo* chronic compressive load alteration applied to the tibio-femoral joint can initiate degenerative changes as evidenced by increased degenerative scoring and diminished cellularity analogous to the early changes occurring in OA. These changes were most pronounced in the medial compartment which experienced an increase in compressive loading. In this work, histological-based metrics of degeneration detected load-induced alterations prior to significant effects on aggregate modulus and permeability.

The VLD rabbit model may be used to study an important risk factor associated with primary OA, increased loading. Overall, the combination of load levels (50 and 80% BW) and load duration (12 and 24 wk) resulted in histological changes in the medial compartment consistent with early OA, including cartilage fibrillation, loss of proteoglycan staining, and diminished cellularity (Fig. 1). Additionally, increased calcified cartilage thickness and focal chondrocyte hypertrophy were observed with increased compressive loading.

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ANTI-INFLAMMATORY EFFECT OF CHONDROMODULATORS IN EXPERIMENT

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Background. There are a few data about the systemic influence of drugs, used in osteoarthritis. A hind limp arthropathy is characterized by progressive cartilage destruction and develops spontaneously in MRL/Mp-lpr/lpr (MRL/l) mice. These mice are a good model for assessment of drugs with chondro-reparitive activity. The ***aim*** of our investigation was to study healing effect of intramuscular injection (IMJ) of chondroitin sulphate (CS) on joint cartilage and tissue lesions.

Material and methods. The age of all animals (60 mice - 30males and 30 females) at the experiment beginning was 5 months. Cartilage, heart, kidney and liver were studied in two groups as follows: the *placebo group*